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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,811	05/14/2001	Robert E. Reiter	02307K-141581	9472

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,811	REITER ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,58-72,74 and 77-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53, 58-72, 74, 77-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. No claims have been amended.

Claims 53, 58-72, 74, 77-97 are pending and under examination.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Response to Arguments

3. The rejection of claims 53, 58-72, 74, 77-97 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained.

The response filed 12/28/04 has been carefully considered but is deemed not to be persuasive. The response states that the experimentation required for practicing the invention may be time-consuming but it is nonetheless routine and the specification teaches administration of immunogenic fragments in prostate cancer cells and PSCA is overexpressed in a number of cancers and the specification teaches how CTL epitopes that bind to HLA alleles can be identified (see page 7-8 of response). In addition, the response cites WO 94/03205 and WO 94/020127 as showing identifying fragments that elicit cellular immune responses and how to evaluate an amino acid sequence for a CTL epitope (see page 8 of response). In response to this argument, first it is noted that the specification may disclose how to find a CTL epitope in PSCA, but there are no such epitopes disclosed. The claims are to specific fragments and it is unpredictable if there

are any CTL epitopes that actually function in the claimed sequences. In response to the WO documents cited WO 94/03205 may show how to identify and screen CTL epitopes, the art clearly shows that it is unpredictable whether those identified by computer actually bind to HLA. This is taught on page 8 stating that the peptides were synthesized and then had to be tested. On page 56, lines 5-7 indicate that the chosen peptide did not have any inhibition. Likewise, Example 12 states that the presence of the motif is necessary but not sufficient for high affinity and only 19% of the identified peptides bound with any affinity needed for therapy (see pages 67-68). This same similar teaching is in the WO 94/020127 which again teaches that one must test each peptide for binding. Thus, while some experimentation is permitted, one has to have a reasonable expectation that one would obtain such a CTL peptide. The specification may disclose how to find such but none are disclosed or if such would be found.

The response further states that US Patent 6,037,135 is directed to methods of making immunogenic peptides that comprise T cell epitopes and the claims set forth such and step (d) defines testing such and therefore the patent is presumed to be enabled (see pages 8-9 of response). In response to this argument, the examiner will not comment on the patent except to say that indeed the method requires testing the complex for binding and as stated previously, one can only determine if one has a CTL motif by testing it. The specification does not teach such motifs or if such actually exist in SEQ ID NO:2.

The response further cites Kiessling et al as teaching CD8+ T cells reactive to two peptides in PSCA (see page 9 of response). In response to this argument, while

two peptides were shown for HLA-A-0201 binding, 8 peptides were originally chosen for testing and only 2/8 bound. The two were from residues 105-113 and 14-22 of PSCA (SEQ ID NO:2). Therefore, only two of the peptides which only were 9 amino acids in length, as opposed to the longer peptides being claimed (minimum about 13 amino acids), resulted in binding. There is nothing in the prior art to indicate that longer peptides as claimed would have the function of binding. In addition, it appears that based on Kiessling et al only the two peptides of residues 14-22, and 105-113 would be enabled and neither of these two peptides specifically are claimed.

The response states that cancer vaccines that elicit cellular immune responses to prostate cancer polypeptides are known and cites references for teaching such (see page 9-10 of response). In response to this argument, Small et al teach that CEA pulsed dendridic cells stimulated an immune response but did not elicit clinical responses in patients with tumors that express CEA (page 3901) and Salgaller et al reported that dendritic cells loaded with antigen fragments of PMSA only stimulated immunity in 2/82 men (see page 3901). Thus, again it appears to be unpredictable whether the dendritic cells pulsed with antigen would produce an immune response that would be an anti-tumor response. With regard to Smith et al, the peptides used were not from the natural antigen they were modified antigen peptides (see page 1562).

In addition, the response also does not address the art cited by the examiner as evidence of undue experimentation such as, Bellone *et al.* (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation

between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Indeed, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells. However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486). In addition just because the protein or peptide is "immunogenic" does not mean it is going to be effective as a antitumor response generator. As stated in Gaiger et al (cited above) the peptide must bind MHC-1 and induce a CTL response (see abstract). In addition, Bellone et al (cited above) states that the peptide should facilitate an effective recruitment of tumor specific CTLs (see page 457). Thus, not just any "immunogenic fragment" will induce the CTLs and be useful as a anti-cancer vaccine as encompassed by the claims. This is underscored by Lu et al (Cancer res 2002 62:5807-12) which teaches computer algorithms predicted five peptides from PSMA that were predicted to induce antigen-specific CTLs, however, only one peptide induced the CTLs that were effective at recognizing prostate tumor cells expressing PSCA (see abstract) and each peptide needed to be tested to determine if it would produce a CTL response (see page 5811).

Therefore, without actually testing the peptides it would be unpredictable whether any of the claimed peptides or protein would function in an anti-tumor cancer vaccine directed against any of the cancers claimed or produce the required CTL response.

All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the protein of SEQ ID NO:2 or immunogenic fragments thereof in pharmaceutical compositions or vaccine formulations as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Conclusion

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

7. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER